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Stereoselective synthesis of novel glyco-pyrano pyrrolidines/pyrrolizidines/indolizidines through intramolecular [3+2] cycloaddition approach

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ABSTRACT

An efficient and stereoselective synthesis of novel furo-pyrano pyrrolidine/pyrrolizidine/indolizidine derivatives has been achieved by intramolecular [3+2] cycloaddition reaction of azomethine ylide generated in situ from *O*-allyl sugar-derived aldehyde and different secondary amino acids.

In recent years, much attention has been focused on the synthesis and development of glycosidase inhibitors[1–6] because of an increasing awareness of the vital role played by carbohydrates in biological processes. Carbohydrates have been used as chiral auxiliaries[7,8] or chiral building blocks in asymmetric transformations due to their known absolute stereochemistry and availability.

Intramolecular 1,3-dipolar cycloaddition reaction with high regio- and stereocontrol[9–12] is an important synthetic tool for the preparation of structurally complex fused heterocyclic ring systems with simultaneous generation of several stereogenic centres. Among them, those involving azomethine ylides[13] constitute an efficient and versatile entry to fused or bridged polycyclic pyrrolidines. Highly substituted pyrrolidines have gained much prominence, since they form the central skeleton of many natural products.[14] In addition, substituted pyrrolidines have biologically important properties as glycosidase inhibitors.[15] Fused *O*-heterocycles, such as furo-pyrans, being constituents of bioactive compounds[16], are also targets for synthesis.

In carbohydrates 1,3-dipolar cycloadditions have gained much attention in recent years. 1,3-dipolar cycloaddition reactions of nitrones and nitrile oxides[17] with alkenes and azides[18] and with alkynes in carbohydrate chemistry are well known in the literature. However, the intramolecular cycloaddition reaction of azomethine ylides derived from carbohydrates for the synthesis of glycoheterocycles is not known and has not been utilized in organic synthesis. In continuation of our work in the area of 1,3-dipolar cycloaddition[19–23], herein we report for the first time the synthesis of 2-cyclohexylidine-octahydro-[1,3]dioxolo[4″,5″,4′,5′]furo[2′,3′:5,6]pyrano[4,3-*b*]pyrrolidine/pyrrolizidine derivatives using intramolecular [3+2] cycloaddition of *O*-allyl sugar-derived aldehyde with cyclic and acyclic amino acids.

As shown in Scheme 1, the construction of a fused pyrrolidine ring system in **3** was envisaged from a [3+2] cycloaddition reaction involving an azomethine ylide with an internal olefin, while templates for such cycloaddition could be conveniently realized from dicyclohexylidine glucose (**1**).

Azomethine ylides can be generated by a number of methods of which the decarboxylation route offers a convenient method for the synthesis of substituted pyrrolidines.[24,25] In this method an aldehyde and a secondary amino acid are condensed to generate the reactive intermediate, which is then trapped by dipolarophiles. This strategy was successfully applied in the present work (Scheme 1).

The reaction of 1,2-*O*-cyclohexylidine-3-*O*-allyl-α-D-xylopentadialdo-1,4-furanose (**2**)[26] with sarcosine (**4**) in refluxing toluene under Dean–Stark conditions furnished cis cycloadduct (**3**) as a major product in 86% yield. The reaction was very rapid and completed in 30 min, as indicated by TLC and proceeded by the in situ generation of azomethine ylide formed by condensation of the aldehyde **2** with sarcosine and cyclized intramolecularly yielding polycyclic pyrrolidine derivative **3** with high diastereoselectivity. The product was purified using silica gel column chromatography (Scheme 2).

The presence of molecular ion peak at $m/z = 296.27$ (M^+) in the mass spectrum confirmed the formation of cycloadduct **3** and this was further confirmed by ^{1}H NMR.

When the same reaction was extended with proline, thiazolidine carboxylic acid, pipecolinic acid and tetrahydroisoquinolinic

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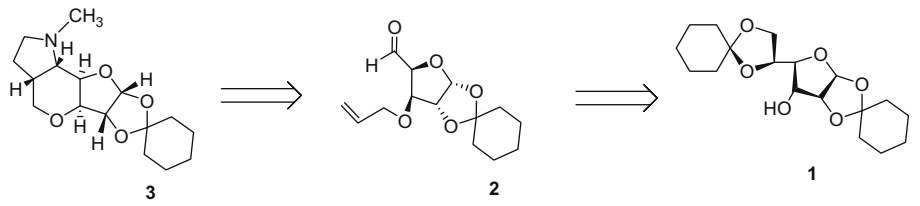
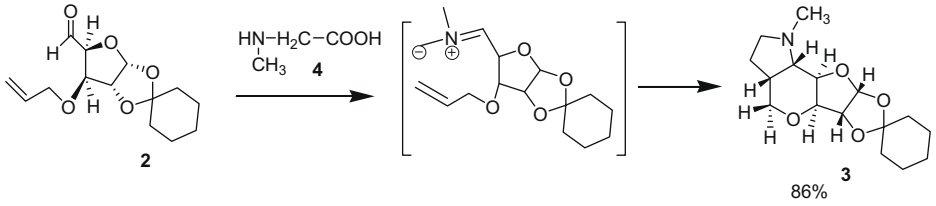


Scheme 1. Retrosynthesis of glyco-pyrrolidines.



Scheme 2. Synthesis of glycopyrrolidines.

acid, we obtained a series of novel pyrrolizidine derivatives in good yield and cycloaddition is totally regio-and diastereoselective, and the formation of cis isomer was observed in all cases (Scheme 3).

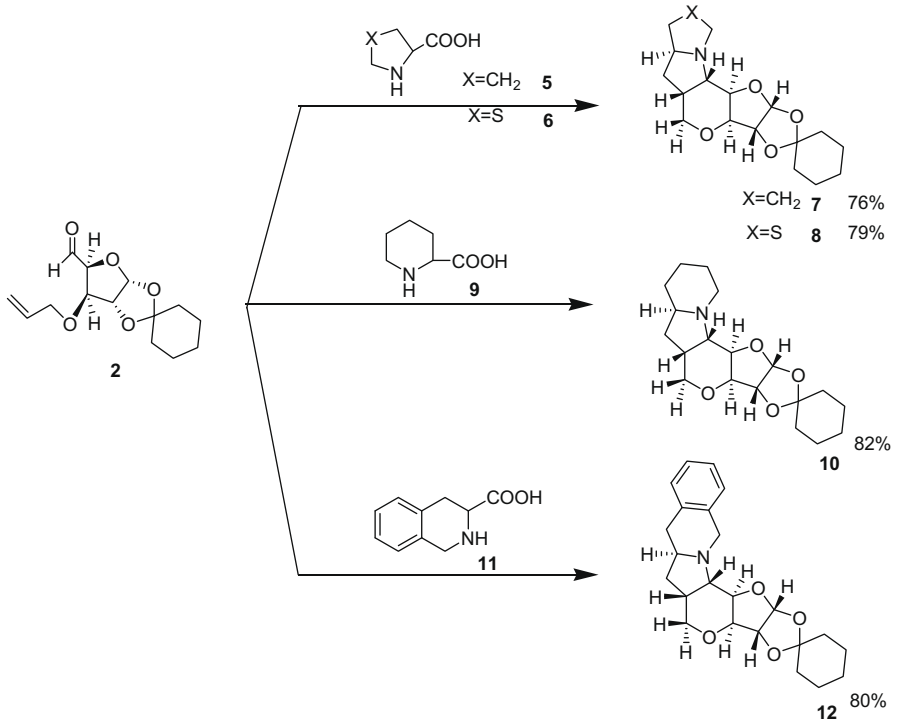
The structure and the stereochemistry of all the products **3**, **7**, **8**, **10** and **12** were determined by analysis of their ^{1}H, ^{13}C, DEPT, $^{1}H–^{1}H$-, $^{1}H–^{13}C$-COSY, ROESY and NOE experiments in the NMR spectrum. The absolute configurations of these compounds were assigned by establishing the relative stereochemistry between the newly formed stereocentre and that already present in the starting material (**2**). The configurations of furan ring carbons of compound (**2**) remained unchanged throughout the performed reactions.

From DEPT, $^{1}H–^{1}H$-, $^{1}H–^{13}C$-COSY experiments, we assigned the signals for the compound **10** as 5.81 ppm to H-13a, 4.44 ppm to H-3a, 4.10 ppm to H-12b, 3.93 ppm to H-3b, 3.37 ppm to H-12a and 2.39 ppm to H-5a (Fig. 1).

In the ^{1}H NMR spectrum of **10**, vicinal coupling of $J_{5a\text{-}5'} = 7.4$ Hz indicates a 1,2-diaxial disposition in a chair conformation.[27] The coupling constant value of $J_{5a\text{-}12a} = 5.57$ Hz suggests that both H-5a and H-12a are *cis* to each other with *S* configuration at C-12a. The signal for the hydrogen H-12a appears as a doublet, which shows that it is coupled to H-5a and not with the vicinal H-12b, indicating that both H-12a and H-12b are on opposite sides, which is further confirmed by ROESY.

In the ROESY spectrum, the proton H-12a showed correlation with the proton H-5a and no correlation with the proton H-12b, suggesting that both H-12a and H-5a are cis to each other, and H-12a is trans to H-12b, likewise H-12b and H-3b cis to each other and H-3b is trans to H-3a and H-3a and H-13a are cis to each other.

The stereochemical assignment was confirmed by NOE experiment. In one dimensional NOE, the selective irradiation of H-12a effected the loss of coupling in the signal of H-5a, H-3a, H-5 and



Scheme 3. Reaction of alkenyl aldehydes with various secondary aminoacids.

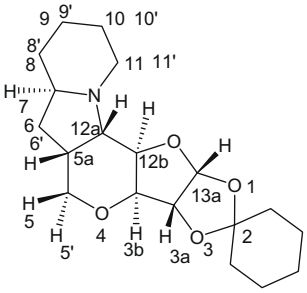


Figure 1. Structure of compound **10**.

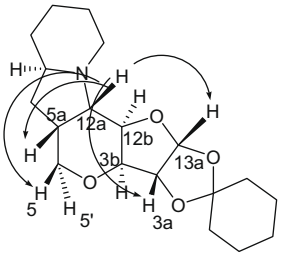


Figure 2. Observed NOE for compound **10**.

H-13a, indicating that these protons are spatially close to each other, which confirms that both H-12a and H-5a are *cis* to each other. Figure 1 summarizes the observed effects for compound **10** (Fig. 2).

In conclusion, we have described a novel, highly efficient and stereoselective method for the synthesis of 2-cyclohexylidine-octahydro-[1,3]dioxolo[4″,5″:4′,5′]furo[2′,3′:5,6]pyrano[4,3:*b*]pyrrolidines/thiopyrrolizidines/pyrrolizidine/indolizidine derivatives through 1,3-dipolar cycloaddition using sugar-derived aldehyde.[28] These compounds may be biologically active due to the presence of glyco-pyrrolidine link. The extension of this work is under progress.

Acknowledgements

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28. *Experimental procedure*: A solution of **1** (1 mmol) and cyclic/acyclic amino acids (1 mmol) in anhydrous toluene (10 ml) was refluxed until the completion of the reaction as evidenced by TLC analysis. The solvent was removed in vacuo and the crude product was subjected to column chromatography on silica gel (100–200 mesh) using petroleum ether/ethyl acetate (9:1) as eluent. *N*-Methyl–2-cyclohexylidine-8a,5a,5,5′,8b,3b,3a,9a-octahydro[1,3]dioxolo [4″,5″:4′,5′] furo[2′,3′:5,6]pyrano[4,3:*b*] pyrrolidine **3**: yield 86%, light yellow colour liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (d, 1H, $J_{9a\text{-}3a}$ = 3.75 Hz, H-9a); 4.41 (d, 1H, $J_{3a\text{-}9a}$ = 3.75 Hz, H-3a); 4.06 (br, 1H, H-8b); 3.91 (br, 1H, H-3b); 3.52 (m, 1H, H-5); 3.14 (t, 1H, H-5′); 2.45 (d, 1H, $J_{8a\text{-}5a}$ = 5.8 Hz, H-8a); 2.30 (s, 3H, N–CH_3); 2.23 (m, 1H, $J_{5a\text{-}8a}$ = 5.8 Hz, H-5a); 1.7-1.25 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.39, 103.92, 83.72, 77.23, 77.13, 72.49, 66.65, 64.39, 55.26, 40.66, 36.34, 35.47, 33.39, 24.89, 23.89, 23.55. MS (EI); *m/z* = 296.27 (M^+). Anal. Calcd for $C_{16}H_{25}NO_4$; C, 65.06; H, 8.53; N, 4.74. Found: C, 65.18; H, 8.64; N, 4.62.
2-Cyclohexylidine-11a,5a,5,5′,11b,3b,3a,12a-octahydro-[1,3]dioxolo [4″,5″:4′,5′]furo[2′,3′:5,6]pyrano[4,3:*b*] pyrrolizidine **7**: yield 76%, light yellow colour liquid, IR (KBr): 3349, 2926, 1079 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (d, 1H, $J_{12a\text{-}3a}$ = 3.6 Hz, H-12a); 4.49 (d, 1H, $J_{3a\text{-}12a}$ = 3.6 Hz, H-3a); 4.17 (br, 1H, H-11b); 4.12 (br, 1H, H-3b); 3.69 (m, 1H, H-5); 3.64 (m, 1H, H-7); 3.39 (t, 1H, H-5′); 3.06 (d, 1H, $J_{11a\text{-}5a}$ = 5.12 Hz, H-11a); 2.81 (m, 1H, H-9); 2.52 (m, 1H, $J_{5a\text{-}1a}$ = 5.12 Hz H-5a); 2.3 (m, 1H, H-9′); 1.72–1.25 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.18, 104.17, 83.53, 76.77, 75.64, 64.36, 66.01, 53.77, 36.62, 36.30, 35.57, 33.93, 32.93, 31.92, 25.31, 24.94, 23.89, 23.58. MS (EI); *m/z* = 322.23 (M^+). Anal. Calcd for $C_{18}H_{27}NO_4$; C, 67.26; H, 8.47; N, 4.36. Found: C, 67.35; H, 8.59; N, 4.26.
2-Cyclohexylidine-11a,5a,5,5′,11b,3b,3a,11a-octahydro-[1,3]dioxolo [4″,5″:4′,5′]furo[2′,3′:5,6]pyrano[4,3:*b*]thio pyrrolizidine **8**: yield 79%, light yellow colour liquid, IR (KBr): 3417, 2925, 1088 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (d, 1H, $J_{12a\text{-}3a}$ = 3.75 Hz, H-12a); 4.49 (d, 1H, $J_{3a\text{-}12a}$ = 3.75 Hz, H-3a); 4.14 (br, 1H, H-11b); 4.11 (m, 1H, H-10); 4.07 (m, 1H, H-5); 4.01 (m, 1H, H-3b); 3.71 (m, 1H, H-7); 3.65 (m, 1H, H-10′); 3.25 (t, 1H, H-5′); 3.15 (d, 1H, $J_{11a\text{-}5a}$ = 5.49 Hz, H-11a); 3.06 (m, 1H, H-8); 2.62 (dd, 1H, H-8′); 2.45 (m, 1H, $J_{5a\text{-}11a}$ = 5.49 Hz, H-5a); 1.76–1.25 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.10, 104.09, 83.14, 76.94, 76.18, 66.59, 66.47, 60.09, 59.12, 40.05, 36.30, 35.50, 34.34, 33.29, 24.94, 23.92, 23.57. MS (EI); *m/z* = 340.27 (M^+). Anal. Calcd for $C_{17}H_{25}NO_4S$; C, 60.15; H, 7.42; N, 4.13. Found: C, 60.28; H, 7.53; N, 4.05.
2-Cyclohexylidine-12a,5a,5,5′,12b,3b,3a,13a-octahydro-[1,3]dioxolo[4″,5″:4′,5′]furo[2′,3′:5,6]pyrano[4,3:*b*]piperidino pyrrolizidine **10**: yield 82%, Light yellow colour liquid, IR (KBr): 3418, 2925, 1088 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (d, 1H, $J_{13a\text{-}3a}$ = 3.6 Hz, H-13a); 4.44 (d, 1H, $J_{3a\text{-}13a}$ = 3.6 Hz, H-3a); 4.10 (br, 1H, H-12b); 3.93 (d, 1H, J = 2.4 Hz, H-3b); 3.58 (q, 1H, $J_{5\text{-}5'}$ = 8.05 Hz, $J_{5\text{-}5a}$ = 4.97 Hz, H-5); 3.37 (d, 1H, $J_{12a\text{-}5a}$ = 5.57 Hz, H-12a); 3.18 (t, 1H, $J_{5'\text{-}5a}$ = 7.4 Hz, $J_{5'\text{-}5}$ = 8.05 Hz, H-5′); 3.09 (m, 1H, H-7); 3.01 (m, 1H, H-11); 2.80 (m, 1H, H-11′); 2.39 (m, 1H, $J_{5a\text{-}12a}$ = 5.57 Hz, $J_{5a\text{-}5'}$ = 7.40 Hz, $J_{5a\text{-}5}$ =4.97 Hz H-5a); 1.67-1.07 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.70, 102.30, 83.12, 75.95, 72.21, 65.95, 57.21, 52.84, 44.18, 35.05, 34.28, 31.33, 31.08, 27.49, 23.65, 22.63, 22.28, 21.31,18.57. MS (EI); *m/z* = 336.33 (M^+). Anal. Calcd for

$C_{19}H_{29}NO_4$; C, 68.03; H, 8.71; N, 4.18. Found: C, 68.20; H, 8.81; N, 4.08.

2-Cyclohexylidine-14a,5a,5,5′,14b,3b,3a,15a-octahydro-[1,3]dioxolo [4″,5″:4′,5′]furo[2′,3′:5,6]pyrano[4,3:*b*] isoquinolino pyrrolizidine **12**: yield 80%, light yellow colour liquid, IR (KBr): 3421, 2933, 1486, 1086 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 7.085–7.199 (m, 4H); 5.81 (d, 1H, $J_{15a\text{-}3a}$ = 3.75 Hz, H-15a); 4.42 (d, 1H, $J_{3a\text{-}15a}$ = 3.75 Hz, H-3a); 4.12 (br, 1H, H-14b); 3.98 (d, 1H, J = 2.4 Hz, H-3b); 3.92 (br, 1H, H-13); 3.62 (m, 1H, $J_{5\text{-}5a}$ = 5.0 Hz, $J_{5\text{-}5'}$ = 7.65 Hz, H-5); 3.59 (br, 1H, H-13′); 3.56 (m, 1H, H-7); 3.22 (t, 1H, $J_{5'\text{-}5a}$ = 9.06 Hz, $J_{5'\text{-}5}$ = 7.65 Hz, H-5′); 2.99 (d, $J_{14a\text{-}5a}$ = 5.60 Hz, 1H, H-14a); 2.79 (dd, 1H, H-8); 2.48 (dd, 1H, H-8′); 2.23 (m, 1H, $J_{5a\text{-}14a}$ = 5.60 Hz, $J_{5a\text{-}5}$ = 5.0 Hz, $J_{5a\text{-}5'}$ = 9.06 Hz, H-5a); 1.216–1.731 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.68, 135.58, 126.65, 126.16, 125.98, 125.24, 111.04, 103.08, 82.46, 76.22, 73.82, 6665.47, 6660.87, 55.11, 49.73, 35.31, 34.42, 32.32, 29.92, 28.68, 23.95, 22.93, 22.57. MS (EI); m/z = 384.50 (M^+). Anal. Calcd for $C_{23}H_{29}NO_4$; C, 72.04; H, 7.62; N, 3.65. Found: C, 72.18; H, 7.73; N, 3.54.